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A New Generation of Nutra-ceuticals and Cosme-ceuticals Complexing Lipophilic Bioactives with γ-Cyclodextrin

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Abstract

We previously reported the bioavailability enhancement of lipophilic Coenzyme Q10 (CoQ10) by complexing with γ-Cyclodextrin (γCD). Here, we report on its mechanism. Hydrophobic CoQ10 generally agglutinates but the dissociated CoQ10 from γCD was captured by bile acid to form nanometer molecular micelle without aggregation and therefore both solubility and bioavailability could be enhanced. Furthermore, we succeeded in the expansion of this finding to personal care field by the use of Dipotassium glycyrrhizate (GZK_2) instead of bile acid. The skin absorptions of actives could be significantly enhanced by the combination of cosme-ceutical-γCD complexes with GZK_2.

Keywords: Cyclodextrin; solubility; bioavailability; association constant; nutra-ceutical; cosme-ceutical

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six, seven and eight glucopyranose residues (α, β and γCDs respectively) bound by α-1,4 glycosidic linkages. CDs have a bucket shape form with a hydrophobic cavity and hydrophilic surface. This unique bucket shape allows inclusion complexes with various hydrophobic substances to improve unfavorable characteristics such as low stability, low water solubility and low bioavailability. Due to the benefits, CDs are frequently used in pharmaceutical formulations. Here not natural CDs but chemically modified CDs are often utilized because of higher water solubilizing power than parent CDs [1-4].

In the contrast, chemically modified CDs cannot be utilized for nutra-ceutical applications from a viewpoint of safety and bioadaptability, because nutra-ceuticals are daily taken for a long period in large

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amount, and some chemically modified CDs have a membrane-perturbing effect, resulting in hemolysis and local irritation at higher doses. Therefore, natural CDs are only alternative CDs to be used for improvement of aqueous solubility and bioavailability of nutra-ceuticals.

In this context, we studied the effect of natural α, β and γCDs on the aqueous solubility and bioavailability of some hydrophobic nutra-ceuticals such as Coenzyme Q10 (CoQ10) [5-7], Curcumin [8, 9], Tocotrienol [10], R-α-Lipoic acid [11], Menaquinone-7 (Vitamin K_2) and Astaxanthin. Complex formations with all natural CDs do not help to enhance aqueous solubility of such nutra-ceuticals in general. But interestingly bioavailability of many kinds of lipophilic bioactives could be significantly enhanced when γCD is especially used.

There are three types of approaches for bioavailability enhancement of bioactives, focusing on maximum plasma concentration of actives (C_{max}) and half life time ($T_{1/2}$) of maximum plasma concentration time (T_{max}) of actives in blood plasma (Fig. 1). One is the C_{max} enhancer. Commercially available "Water soluble CoQ10" formulation using fatty oil based emulsifier is known as one of the typical examples for enhancing C_{max} but without giving prolongation of $T_{1/2}$ in comparison with the dotted line for the general CoQ10 formulation (Type 1) [12]. The other type of the aides works to prolong $T_{1/2}$. For example, the glucosidated bioactives like ascorbic acid 2-glucoside give $T_{1/2}$ prolongation of ascorbic acid due to slow cleavage of glucose bond by glycosdase in intestine [13]. But due to the slow release of the bioacitive into blood, C_{max} becomes somewhat lower (Type 2). In comparison with those approaches, the inclusion complex formation of hydrophobic substances with γCD can work for both enhancing C_{max} and prolonging $T_{1/2}$ and therefore gives the highest area under the blood concentration-time curve (AUC) (Type 3).

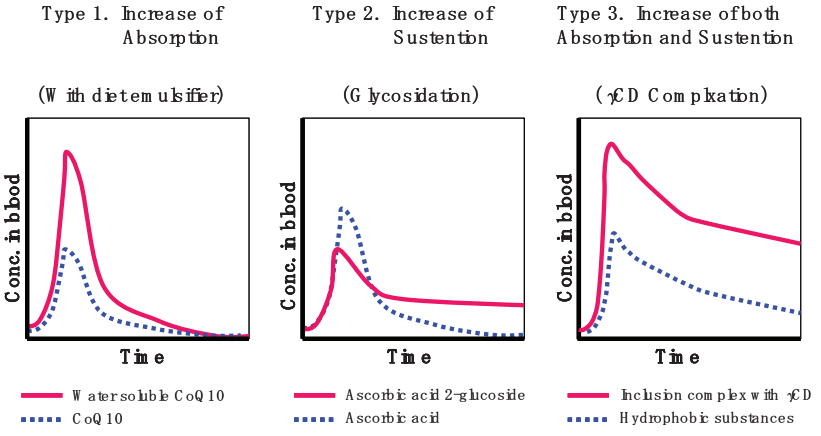

Fig. 1. 3 types of bioavailability enhancement by Cyclodextrin. —Absorption and sustention in blood—

For example, we have previously reported the bioavailability enhancement of hydrophobic CoQ10 by the complexation with γCD which showed unique profile along the line with Type 3. CoQ10 concentration changes in blood plasma were evaluated after oral administrations by three different formulations, CoQ10-γCD complex, CoQ10 with fatty oil based emulsifier so called "water soluble CoQ10" and CoQ10-micro crystalline cellulose (MCC) mixture on fasted human subjects. The administration of CoQ10-γCD complex showed the highest C_{max} and the longest $T_{1/2}$ of CoQ10 in blood plasma among three formulations as shown in Fig. 2.

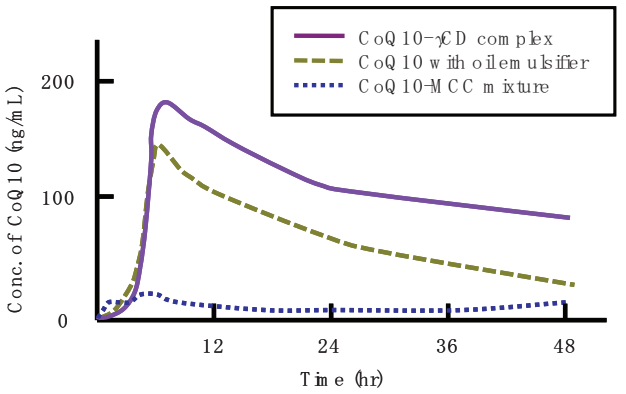

Fig. 2. Time course of plasma level of CoQ10 after an oral administration of CoQ10 with 3 different formulations, CoQ10-γCD complex, CoQ10 with oil emulsifier and CoQ10-MCC mixture for 72 healthy adult subjects (CoQ10 intake: 30 mg per subject).

In the beginning of our study on bioavailability of CoQ10-γCD complex, we did not have any clear explanations for the mechanism why significantly enhanced bioavailability of CoQ10 could be observed in spite of poorly aqueous soluble characteristics of CoQ10-γCD complex. However, we have recently found the most plausible explanation which includes the significant increase of the aqueous solubility of CoQ10 with the aid of sodium taurocholate (Na TCA) as a constituent of bile acid in small intestine.

CoQ10-γCD complex has extremely poor water solubility. But the water solubility of CoQ10 could be significantly improved by the addition of Na TCA to CoQ10-γCD complex. Its plausible mechanism is as follows. A water soluble Na TCA-γCD complex was formed by substituting the guest molecule from CoQ10 to Na TCA which has higher association constant with γCD than CoQ10. The association constants of γCD complex with Na TCA and CoQ10 are respectively 3100 M^{-1} and 2200 M^{-1} [14]. CoQ10 molecule dissociated from γCD complex could be solubilised in water captured one by one in the midst of Na TCA micelle, in other words, “molecular captured micelle” whereas hydrophobic CoQ10 molecule agglutinates in water to form visible particles in general.

The aqueous solubility of CoQ10 by this method was ca. 100 times higher than that of commercially available oil emulsifier formulation “water soluble CoQ10” whose particle size was controlled around 100 nm in diameter. By the formation of “molecular captured micelle”, it is thought that the significant high AUC could be observed via effective absorption into intestinal epithelial cells on the molecular level. This method could be applied for not only CoQ10 but also the other nutra-ceuticals like Curcumin, Tocotrienol, Vitamin K_2 and R-α-Lipoic acid having human health benefits.

In the wake of the breakthrough project using CoQ10-γCD complex and Na TCA, we could also establish this new molecular captured micelle formulation system in cosme-ceutical field by the combination of γCD complex with dipotassium glycyrrhizate (GZK_2) which has high association constant and possesses hydrophilic region to form water soluble GZK_2 complex as well as Na TCA (Fig. 3) [15, 16]. Here we observed much higher CoQ10 intake into a human epidermis structure model by the formulation of CoQ10-γCD complex with GZK_2 compared to the other cosmetic formulations for example using liposome and fatty oil based emulsifiers.

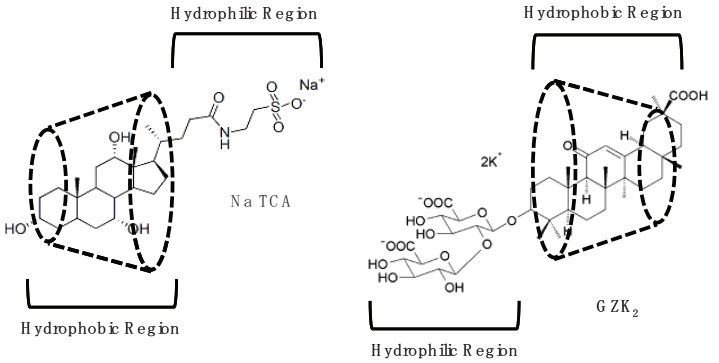

Fig. 3. The structures of Na TCA and GZK_2 γCD complexes.

2. Study on solubility enhancing effects of hydrophobic bioactives by adding Na TCA or GZK_2 to γCD complex

2.1. Materials

CoQ10 was obtained from Mitsubishi Gas Chemical Company, Inc. CoQ10-γCD complex containing 20 % (wt/wt) CoQ10 was supplied from Wacker Chemical Corporation (Adrian, Michigan) as product named CAVAMAX® W8 CoQ10. CoQ10-αCD complex and CoQ10-βCD complex were prepared by a conventional spray-dry method. GZK_2 was donated by Tokiwa Phytochemical Co., Ltd. Na TCA was purchased from Wako Pure Chemical Industries, Ltd. 1-Adamantane carboxylic acid (AdCA) was purchased from Tokyo Chemical Industries, Ltd.

Curcumin-γCD complex containing 14 % (wt/wt) of curcuminoids was supplied from Wacker Chemical Corporation (Adrian, Michigan) as product named CAVAMAX® W8 Curcumin.

2.2. Water solubility changes of CoQ10 by various CoQ10 formulations

Adding effect of Na TCA to CoQ10-γCD complex on water solubility enhancement of CoQ10: CoQ10 concentrations for four types of formulated CoQ10 samples prepared as described below were measured by HPLC. Shimadzu HPLC system (LC-2010C) was used for the measurement of CoQ10 concentration in the aqueous solution. Phenomenex HPLC column (Luna 5u C18(2) 100A : 4.6 mm I.D. x 150 mm) was used. Column temperature was set at 35°C. A mixture of methanol, ethanol and distilled water (60 : 40 : 1) was used as mobile phase with the flow rate of 0.8 mL/min. CoQ10 was detected using UV detector at 275 nm.

1) CoQ10-γCD complex with Na TCA: A mixture of 33 mg of Na TCA with 60 mg of CoQ10-γCD complex containing 12 mg of CoQ10 was added into 3 mL of Milli-Q water. 2) CoQ10-γCD complex: 60 mg of CoQ10-γCD complex containing 12 mg of CoQ10 was added into 3 mL of Milli-Q water. 3) Water soluble CoQ10: To a solution of 33 mg of N-cocoyl-L-arginine ethyl ester-DL-pyrrolidone carboxylate salt (CAE) as amino acid cationic surfactant in 3 mL of Milli-Q water, 12 mg of CoQ10 was added. 4) Pure CoQ10: 12 mg of CoQ10 was added to 3 mL of Milli-Q water. The resultant suspensions were

sonicated for 30 min and filtrated through 0.2 μm PTFE filter to get transparent solution containing CoQ10.

Results and Discussions: CoQ10 is poorly soluble in water due to its lipophilic side chain constructed with 10 mono-unsaturated trans-isoprenoid units. Even after sonication, the water solubility was only 0.3 μg/mL. The complex formation with γCD did not help so much to enhance the water solubility of CoQ10. Its CoQ10 concentration was 2.9 μg/mL. On the other hand, the addition of Na TCA to CoQ10-γCD complex assisted a great deal of the solubility enhancement of CoQ10. In fact, adding Na TCA to the cloudy water suspension of CoQ10-γCD complex, it was observed to be transparent clear solution. The CoQ10 concentration of the solution obtained from the formulation of CoQ10-γCD complex with Na TCA was surprisingly high at 1147.5 μg/mL, which is more than 100 times higher than that of "water soluble CoQ10" formulation using amino acid cationic surfactant, CAE (11.4 μg/mL) as shown in Fig. 4.

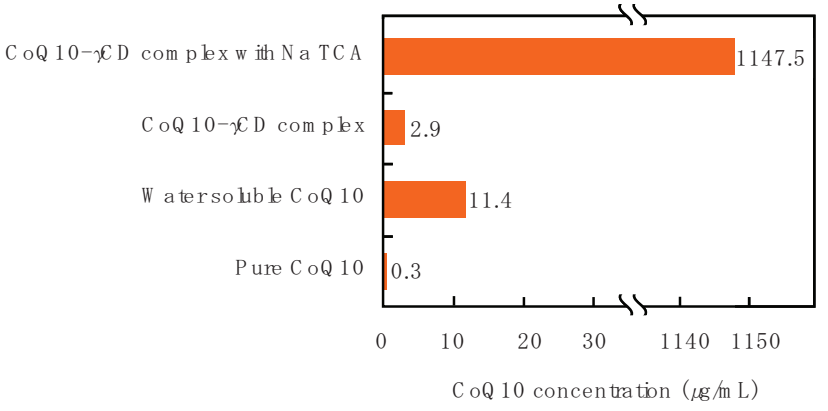

Fig. 4. Water solubility changes of CoQ10 by 3 different formulations in comparison with CoQ10-γCD complex with Na TCA, CoQ10-γCD complex, water soluble CoQ10 formulation using amino acid cationic surfactant, CAE, pure CoQ10.

The role of Na TCA for this significant solubilizing effect is thought to be due to the formation of water soluble Na TCA-γCD complex by substituting the guest molecule from CoQ10 to Na TCA which has higher association constant with γCD than CoQ10, followed by the formation of molecular captured micelle of dissociated CoQ10 with Na TCA. The structure of Na TCA can be divided into hydrophilic region and hydrophobic region. The hydrophobic region is entrapped by excellent fit in γCD cavity. The hydrophilic region is placed outside of the cavity and is accordingly thought to be the reason for the high water solubility of Na TCA-γCD complex. GZK_2 is also known to form water soluble complex with γCD due to the similar structure to Na TCA as described in Fig. 3. Therefore, in order to pursue whether our conjecture is right or not, our second study was the evaluation of the water solubility changes of CoQ10 by the addition of GZK_2 to CoQ10-γCD complex compared with just a mixture of pure CoQ10 with GZK_2. The water solubility of CoQ10 was not enhanced at all by adding GZK_2 to the suspension of pure CoQ10 in water. But by adding GZK_2 to CoQ10-γCD complex suspension, the water solubility of CoQ10 increased with increasing added GZK_2 amount. Significantly high CoQ10 water solubility (more than 2000 μg/mL) was achievable by higher GZK_2/CoQ10 molecular ratio than 10. The results might show that only one molecule of GZK_2 is required for the formation of GZK_2-γCD complex but around 10 molecules of GZK_2 are essential for solubizing one molecule of dissociated CoQ10 by the formation of molecular micelle of GZK_2 entrapping CoQ10.

2.3. Water solubility enhancement of CoQ10 by adding GZK_2 and AdCA to three CoQ10-natural CD complexes

Adding effect of GZK_2 on water solubility enhancement of CoQ10 to three natural CD complexes: CoQ10-CD complex (10 mg) was weighed in a vial. GZK_2 (molar ratios against CoQ10 are 0, 3, 5, 7, 10, 20, 30 and 40) were added in the vials, followed by addition of Milli-Q water (5 mL). The resultant suspensions were sonicated for 30 min, and filtrated through 0.2 μm PTFE filter to get transparent solution containing CoQ10. The concentrations of CoQ10 for all samples were measured by HPLC. The same Shimadzu HPLC system (LC-2010C) was used as above experiment.

Influence by adding AdCA to the water solubility enhancing system by the combination of CoQ10-CD complexes with GZK_2: CoQ10-CD complex (10 mg) was weighed in a vial. GZK_2 (molar ratios against CoQ10 are 0, 3, 5, 7, 10, 20, 30 and 40) and AdCA (10 mg) were added in the vials, followed by addition of Milli-Q water (5 mL). The resultant suspensions were sonicated for 30 minutes, and filtered through 0.2 μm PTFE filter to get transparent solution containing CoQ10. Then, the concentrations of CoQ10 for all samples were measured by HPLC.

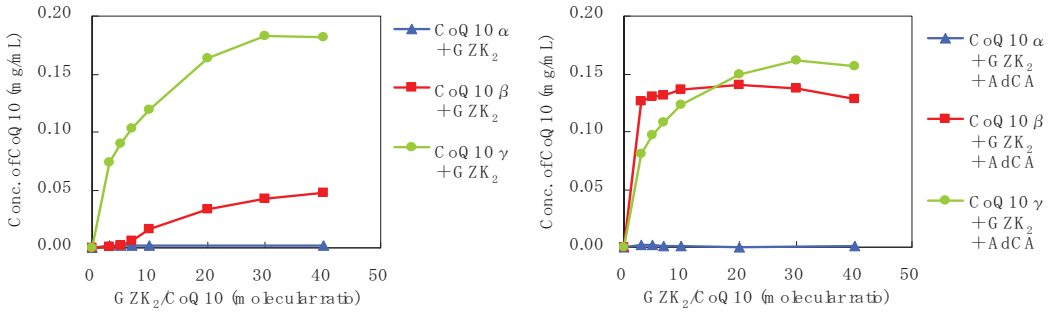

Fig. 5. Water solubility changes of CoQ10 by the combination of three CoQ10-natural CD complexes with GZK_2 (left line graph) and with GZK_2 and AdCA (right line graph).

Results and Discussions: The water solubility changes of CoQ10 by the combination of CoQ10-three natural CD complexes with GZK_2 were shown in the left line graph of Fig. 5. Increasing molecular ratio of GZK_2 to CoQ10 gives outstanding higher CoQ10 concentration in case of the combination of CoQ10-γCD complex (CoQ10γ) with GZK_2, whereas no significant increase could be observed using CoQ10-αCD complex (CoQ10α) and CoQ10-βCD complex (CoQ10β). This excellent solubility enhancing effect of GZK_2 is thought to be due to high association constant of GZK_2 with γCD to form GZK_2-γCD complex by substituting the guest molecule from CoQ10 followed by the formation of CoQ10 molecular captured micelle with GZK_2. The association constants of GZK_2 with αCD and βCD are relatively too low to substitute CoQ10 for the formation of GZK_2-CD complexes.

AdCA is known to have extremely high association constant with βCD as well as the association constant between GZK_2 and γCD [17]. Then, our next evaluation was the adding effect of AdCA on the water solubility changes of CoQ10 by the combination of three natural CD complexes with GZK_2. As shown in right line graph of Fig. 5, the significant increase of CoQ10 concentration was observed by the addition of AdCA to CoQ10-βCD complex (CoQ10β) with GZK_2 with almost same CoQ10 concentration increasing ratio by the combination of γCD complex with GZK_2. We believe that this observation supports our plausible explanation mechanism for the formation of GZK_2-γCD complex or AdCA-βCD complex, followed by CoQ10 molecular captured micelle formation with GZK_2.

2.4. Water solubility enhancement of Curcumin by adding Na TCA to its γCD complex

Sample Preparation: 1) Addition of Na TCA to physical mixture of Curcumin with γCD: 6.6 mg of Curcumin and 43 mg of γCD were added into 2 mL of deionized water with the calculated amount of Na TCA (molar ratio of γCD to Na TCA is 1 : 2) in a micro tube. 2) Addition of Na TCA to Curcumin-γCD complex: 50 mg of Curcumin-γCD complex containing 6.6 mg of Curcumin was weighed and added into 2 mL of deionized water containing calculated amount of Na TCA (molar ratio of γCD in the complex to Na TCA is 1 : 2) in a micro tube. 3) Addition of Na TCA to Curcumin: 6.6 mg of the Curcumin was added into 2 mL of deionized water containing Na TCA in a micro tube. Three of resultant suspensions were then physically mixed well and used for the measurements. 4) Curcumin-γCD complex without adding Na TCA as a comparison sample, was just dispersed in deionized water and used for the measurement.

Measurement of Curcumin content: Shimadzu HPLC system (LC-2010C) was used for the measurement of Curcumin fixing Sunfire HPLC column (ODS: 4.6 mm I.D. x 100 mm). The column temperature was set at 40°C. Mobile phase of 10 mM NaH_2PO_4 (pH 2.6) : MeOH = 3 : 7 was used at the flow rate of 0.8 mL/min. Curcumin was detected using UV detector at 430 nm.

Results and Discussions: The aim of this study is to evaluate the generality of our findings with regard to the water solubility and bioavailability enhancements of lipophilic bioactives by molecular captured micelle formation technology using γCD. Curcumin in turmeric has attracted a lot of attention of researchers in the fields of Alzheimer's disease, memory deficits, arthritis, cancer, including breast cancer and diabetes because of its strong antioxidant and anti-inflammatory characteristics. But Curcumin is a lipophilic substance and hard soluble in water so that it is known to have extremely low bioavailability as same as CoQ10. H. Reuscher studied the bioavailability enhancement of Curcumin by the administration of Curcumin-γCD complex in vivo on rats [18]. According to his study, the concentration of Curcumin in blood plasma was raised up very much after single administration of Curcumin-γCD complex showing extremely high AUC and C_{max} whereas only slight increase of Curcumin concentration in blood plasma was shown after the administration of commercially available Curcumin formulation using oil emulsifier advocating high bioavailability as shown in Fig. 6.

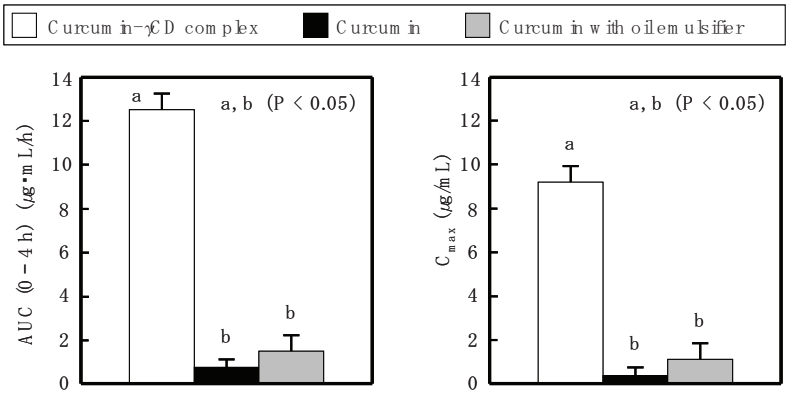

Fig. 6. Bioavailability enhancement of Curcumin by single administration of Curcumin-γCD complex to rats (Curcumin content: 500 mg/kg weight).

In the same manner as the evaluation for CoQ10, -γCD complex, we evaluated the water solubility enhancement by the combination of Curcumin-γCD complex with Na TCA. The complex formation of

Curcumin with γCD or just the addition of Na TCA to Curcumin did not help to enhance the solubility of Curcumin in water at all. But as we anticipated, by adding Na TCA to not physical mixture of Curucumin with γCD but Curcumin-γCD complex, the water solubility of Curcumin was significantly enhanced (Fig. 7). We believe that our results show the reason of bioavailability enhancement of Curcumin which is due to the aid of bile acids in small intestine of rats. The absorption of Curcumin was enhanced by the formation of Curcumin molecular captured micelle with bile acids after releasing from its γCD complex.

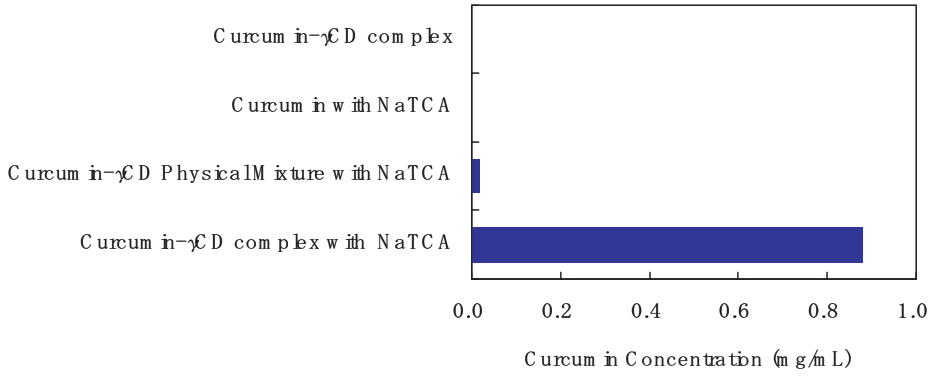

Fig. 7. Water solubility changes of Curcumin by 4 different formulations, Curcumin-γCD complex, Curcumin with Na TCA, physical mixture of Curcumin+γCD with Na TCA, Curcumin-γCD complex with Na TCA.

3. In vitro study on epidermis absorption enhancing effect of CoQ10 by adding GZK_2 to its γCD complex

3.1. Materials

The human three-dimensional cultured epidermal model "LabCyte EPI-MODEL" was purchased from Japan Tissue Engineering Co., Ltd. This is multi-layered epidermal model cultured by using normal human skin cells. It consisted of multiple and viable cell layers and contained basal layer, stratum spinosum epidermidis, granular layer and stratum corneum. It's characterized by the morphological resemblance to human skin. Since human cells are utilized, the test result could be extrapolated to the actual human skin response. Test results are reproducible because of small well-to-well and lot-to-lot variation (Fig. 8) [19]. Since cells maintain metabolic activity, it can also be applied to the pharmacological test of various drugs, cosmetics and so on. Liposome CoQ10 was obtained from Croda Japan KK.

3.2. Methods, Results and Discussions

The tissue cultures were preincubated for 18 h at 37°C in 5 % CO_2 environment. Then the tissues were placed into well plate with 1 mL assay medium dispensed. After each 0.2 mL test materials were added to the tissues, they were incubated for more than 6 h at 37°C in 5 % CO_2 environment. The tissues were rinsed five times with 1 mL of 0.1 M phosphate buffered saline (PBS). The content of absorbed CoQ10 in the tissues was extracted with 5 mL of chloroform : methanol (1 : 1) by shaking for 30 min. Then extracted solvent was evaporated by using centrifugal concentrator. After drying, to the evaporated

residue was added 0.7 mL ethanol including 0.1 mL of iron chloride in ethanol solution (1 mg/mL) as oxidizing reagent. It was filtered through 0.2 μm PTFE filter, and its CoQ10 content in the tissue culture was analyzed by Shimadzu LCMS system (LCMS-2020). Phenomenex HPLC column (Luna 5u C18(2) 100A : 4.6 mm I.D. x 150 mm) was used. Column temperature was set at 35°C. The mobile phase was used with a mixture of acetonitrile and isopropanol (8 : 7) containing 0.5 % formic acid and 0.1 % trisodium citrate aqueous solution (1 mg/mL), with the flow rate of 0.2 mL/min. The mass spectrometer fitted with an electro spray ionisation (ESI) source was used for analysis. It was operated in the positive ion mode with the following parameters: probe voltage +4.50 kV (+ESI), nebulizer gas flow 1.5 L/min, drying gas flow 15.0 L/min, block heater 200°C, DL temperature 250°C.

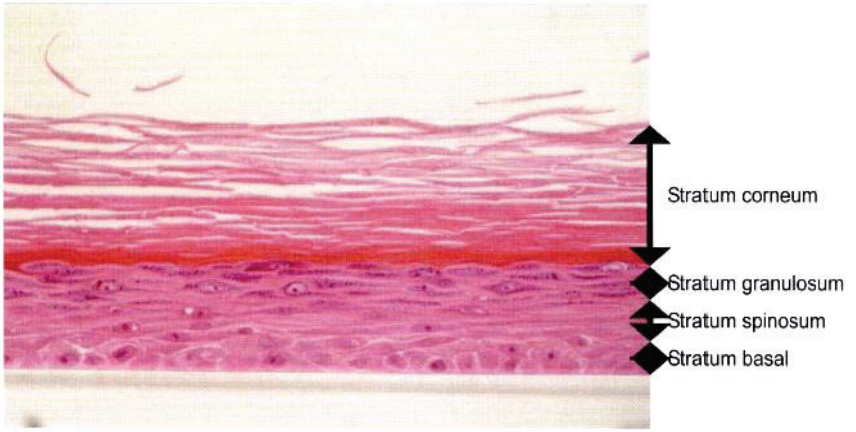

Fig. 8. Histological cross-sectional views of LabCyte EPI-MODEL with H&E staining.

Preparation of samples: 60 mg CoQ10-γCD complex containing 12 mg of CoQ10 and 33 mg of GZK_2 were added into 3 mL of Milli-Q water. The resultant suspension was sonicated for 30 min, and filtered through 0.2 μm PTFE filter. The concentration of CoQ10 in the aqueous solution was ca. 1000 μg/mL. The suspensions of pure CoQ10, CoQ10-γCD complex and physical mixture of CoQ10 with GZK_2 were prepared without filtering as comparative samples containing 1000 μg/mL of CoQ10.

Results and Discussions: CoQ10 absorption study using an in vitro digestion-Caco-2 cell model has already been reported by H. N. Bhagavan et al. In their study, various commercially available CoQ10 formulation products were subjected to simulated digestion to mimic their passage through the gastrointestinal tract to generate micelles containing CoQ10 and bile acids like taurocholate [20]. The micelles prepared from the CoQ10 formulation products were added to monolayers of Caco-2 cells to determine the amounts of CoQ10 uptake. Their data demonstrated significantly enhanced uptake of CoQ10 from CoQ10-γCD complex as compared with pure CoQ10 powder and the other formulations. Here we had similar results using in vitro human epidermis structure model as well as Caco-2 cell model. Outstandingly high CoQ10 uptake in the tissue culture of human epidermic cell (keratinocytes) was observed when a solution prepared from CoQ10-γCD complex with GZK_2 is applied in comparison with the other usual cosmetic formulations using liposome and fatty oil based emulsifiers (Fig. 9).

The processes of aging and photo-aging are associated with an increase in cellular oxidation. This is in part due to a decline in the levels of the endogenous cellular antioxidant CoQ10. U. Hoppe et al. demonstrated that topical application of CoQ10 is effective against UVA mediated oxidative stress in human keratinocytes [21]. Furthermore, the topical application of CoQ10 was able to significantly

suppress the expression of callagenase in human dermal fibroblasts to be effective to reduce wrinkle depth. But higher concentration of CoQ10 than 0.3 wt % in cosmetic formulation was required in order to have the efficacy to prevent many of detrimental effects of photo-aging in spite that upper limit of CoQ10 concentration is restricted to be 0.03 wt % in cosmetics in Japan. Accordingly our finding may contribute the developments of effectual photo-aging care products containing CoQ10.

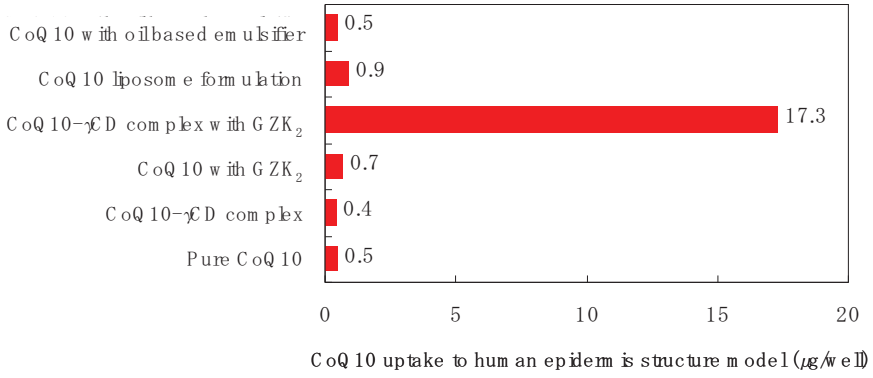

Fig. 9. Uptake changes of CoQ10 into human epidermis structure model by using various CoQ10 formulations, CoQ10 with oil based emulsifier (commercial product), CoQ10 liposome formulation (commercial product), CoQ10-γCD complex with GZK_2, CoQ10 with GZK_2, CoQ10-γCD complex, pure CoQ10.

4. Conclusions

Natural lipophilic bioactives possessing human health benefits like CoQ10 have some unfavorable characteristics for use as nutra-ceuticals and cosme-ceuticals in general. They are usually unstable against oxygen, ultraviolet light and heat. Their water solubility is low due to the hydrophobic nature which causes its low bioavailability to our human body. Therefore we focused on the systematically studies regarding the improvements of low stability, low water solubility and low bioavailability of lipophilic bioactives by the complexation with γCD and finally discovered new nanotechnology by the formation of "molecular captured micelle" as a breakthrough of our studies. The water solubility and bioavailability enhancing mechanism is as follows; When Na TCA or GZK_2 is added to a water dispersion of CoQ10-γCD complex, the guest molecule, CoQ10 is substituted by Na TCA or GZK_2 whose association constant is higher than CoQ10 followed by the formation of water soluble Na TCA- or GZK_2-γCD complex. The dissociated CoQ10 molecules are surrounded by surface-active Na TCA or GZK_2 to form a few nanometer size molecular captured micelles. The water solubility of CoQ10 could be greatly enhanced by this molecular captured micelle formation with GZK_2. It is therefore supposed to contribute the excellent permeability of CoQ10 into epidermis. The bioavailability enhancement can be explained in the same way. Nano-size micelles of commercially available "Water soluble CoQ10" using fatty oil based emulsifiers are the micelles to which CoQ10 flocculates with more than 100 nm diameter. Since bile acid has the same property as GZK_2 for molecular substitution of γCD complex, it is easily imaginable that CoQ10 molecules form bile acid micelles and as the result the absorption of CoQ10 in the intestine is enhanced (Fig. 10).

This innovative molecular captured micelle formation nanotechnology introduced here, useful for the enhancement of bioavailability and epidermis permeability, is applicable for not only CoQ10 but also the other lipophilic bioactives such as Curcumin, R-α-Lipoic acid and Tocotrienol.

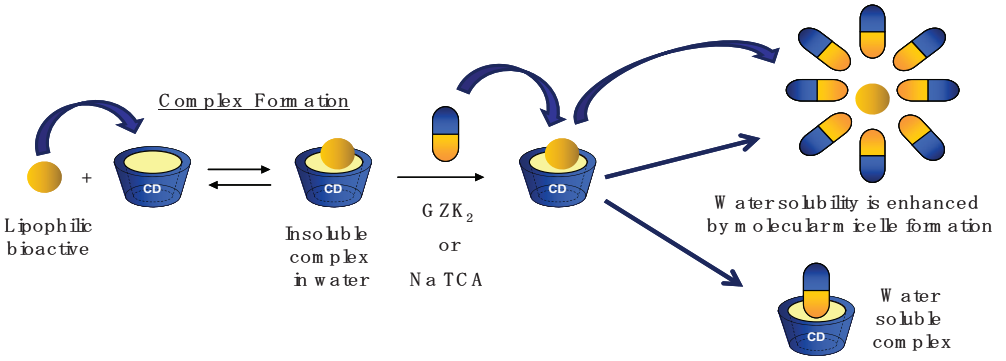

Fig. 10. Proposed mechanism for the formation of "molecular captured micelle". When Na TCA or GZK_2 is added to a water dispersion of lipophilic bioactive-CD complex, the guest molecule is substituted by Na TCA or GZK_2 whose association constant is higher than the guest molecule followed by the formation of water soluble Na TCA- or GZK_2-γCD complex. The dissociated guest molecules are surrounded by surface-active Na TCA or GZK_2 to form "molecular captured micelles"

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